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Silver-Mediated *exo*-Selective Tandem Desilylative Bromination/Oxycyclization of Silyl-Protected Alkynes: Synthesis of 2-Bromomethylene-Tetrahydrofuran

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Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Tandem reactions are one-pot multi-step processes and are thus among the most useful synthetic methods.[1] Recently, the use of transition metals in tandem reactions has received considerable attention and has revolutionized the synthetic strategies in organic chemistry.[2] Among the transition metal-based tandem reactions, the processes that involve heterocyclization reactions of unsaturated substrates are of particular interest,[3,4] as they provide a direct method for the construction of synthetically and biologically valuable heterocycles.

The intramolecular heterocyclization of γ or δ-hydroxyalkynes promises to be a convenient way to access the functionalized tetrahydrofurans and pyrans, which are common motifs in a variety of natural products. This cyclization can be driven by transition metal catalysts, and the regioselectivity of these reactions varies depending on the metal and the conditions employed.[5] Among the metals thus far reported for these reactions, silver and gold have been demonstrated to be the most effective and selective for the formation of *exo*-dig products.[6,7] These metals can promote heterocyclization of both internal and terminal alkynes. Even halogenated and silylated alkynes can be converted into the corresponding *exo*-dig products using these metals.

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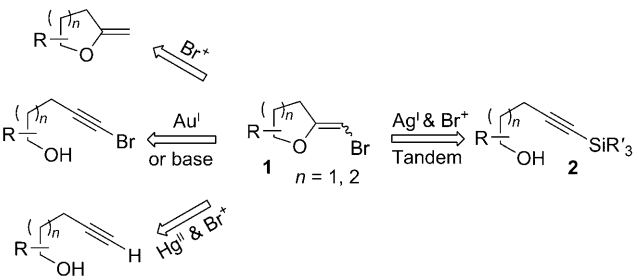
The exocyclic enol ether function, created by the *exo*-dig heterocyclization of hydroxyalkynes, is synthetically useful because it is amenable to further chemical transformations, such as hetero-Diels–Alder reactions and electrophilic additions.[8] In the synthesis of functionalized oxygen heterocycles, the exocyclic β-bromo enol ether **1** (Scheme 1) is more



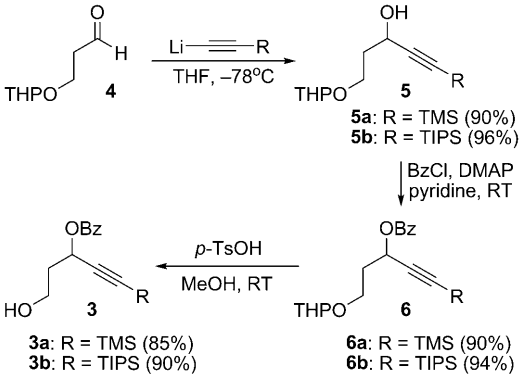
Scheme 1. Formation of the exocyclic β-bromo enol ether (**1**).

useful due to the presence of an additional functionality, the vinyl halide moiety. As shown in Scheme 1, this functionality can be accessed from the exocyclic enol ether by bromination.[9] In addition, it can be directly produced by the intramolecular heterocyclization of bromoacetylenic alcohols in the presence of a gold catalyst or base.[5d,10] Mercury-induced heterocyclization of an acetylenic alcohol followed by interception of the resulting organomercury intermediate using *N*-bromosuccinimide (NBS) also leads to the formation of β-bromo enol ethers.[11]

We envisioned that the exocyclic β-bromo enol ether functionality could be accessed directly from the silylacetylenic alcohol **2** through tandem silver(I)-mediated desilylative bromination and heterocyclization.[12] In addition to promoting the heterocyclization of hydroxyalkynes, silver also has the ability to induce the in situ one-pot desilylative bromination of silyl-protected acetylenes. The trimethylsilyl

(TMS)-protected acetylenes can be converted into haloacetylenes through the use of a catalytic amount of $AgNO_3$ and a halogen source, such as NBS or *N*-iodosuccinimide (NIS).[13] Acetylenes with a bulky silyl group, such as *tert*-butyldimethylsilyl (TBDMS) and triisopropylsilyl (TIPS), can also be transformed into bromoacetylenes in the presence of AgF and NBS.[14] Thus, the employment of silver would allow the desired tandem transformation to produce the synthetically useful exocyclic β-halo enol ether functionality from the readily obtainable silyl-protected acetylenic alcohols. Herein, we report our studies on this subject and describe the total synthesis of pachastrissamine from the tandem product to demonstrate the potential of the developed synthetic method.

We chose to study substrate **3** (Scheme 2) as a model, which contains an oxygen atom at the propargylic position. The interaction between the propargylic C–O bond and the

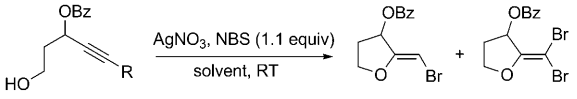


Scheme 2. Synthesis of the silyl-protected acetylenic alcohol **3**.

adjacent triple bond has been reported to alter the electron density of the π system and affect the metal–alkyne coordination and eventually the heterocyclization step.[15] As the electronic influence of the propargylic substituent can be examined by changing the benzoate protecting group of **3** to the electron-donating protecting group (see below), substrate **3** is a suitable initial model for testing the feasibility of the silver(I)-mediated tandem reaction and evaluating the scope of these reactions. The silyl-protected acetylenic alcohol **3** was prepared from the known aldehyde **4**[16] by the addition of lithium acetylide, protection of the resulting propargylic alcohol, and deprotection of the primary alcohol (Scheme 2).

The tandem desilylative bromination/oxycyclization was initially conducted with the TMS-protected acetylene **3a**. Our first attempts to accomplish the silver-mediated tandem reactions of **3a** involved employing the NBS/$AgNO_3$ conditions.[13] Treatment of **3a** with the conventional catalytic amount of $AgNO_3$ (0.1 equiv) and a slight excess of NBS (1.1 equiv) in acetone (Table 1, entry 1) led to the desired tandem bromination/oxycyclization. The reaction was completed in seven hours and yielded only the *exo*-dig products. However, these reaction conditions produced a mixture of

Table 1. $AgNO_3$-mediated bromination/oxycyclization of TMS-protected acetylene **3a** and terminal acetylene **9**.



3a: R = TMS
9: R = H
7 **8**

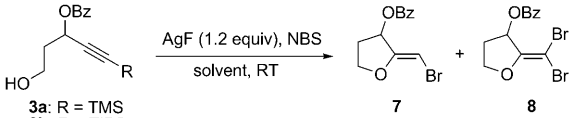
Entry	Substrate	$AgNO_3$ [equiv]	Solvent	*t* [h]	Combined yield [%][a]	**7**:**8**[b]
1	**3a**	0.1	Acetone	7	70	49:51
2	**3a**	1.2	Acetone	2	72	52:48
3	**3a**	0.1	MeCN	48	NR[c]	–
4	**9**	0.1	Acetone	3	72	67:33
5	**9**	1.2	Acetone	1	73	71:29

[a] Yields determined by GC analysis. [b] Product ratio was determined by GC and ^{1}H NMR spectroscopic analyses. [c] Starting material **3a** was primarily recovered.

an almost equal ratio of the β-bromo enol ether **7** and the β-dibromo enol ether **8** in 70% combined yield. The obtained enol ether **7** has the *Z* stereochemistry, which was determined by NOESY analysis. An increase in the amount of $AgNO_3$ beyond one equivalent did not significantly alter the ratio of the two products (entry 2). The same reaction in acetonitrile did not proceed well (entry 3). When the terminal acetylene **9** was employed as a substrate, the tandem reaction also afforded a mixture of **7** and **8** with low selectivity (entries 4–5).

After initial feasibility studies with $AgNO_3$, we then proceeded to AgF as a silver ion source. Exposure of the TMS-protected acetylene **3a** to AgF (1.2 equiv) in the presence of a slight excess of NBS (1.1 equiv) in acetonitrile resulted in selective formation of the mono-bromo product **7** as the major product (Table 2, entry 1). Only a small amount of the bis-bromo product **8** was detected. When this system was applied to the terminal acetylene **9**, the selectivity was also very high (entry 2). Under these reaction conditions, even the acetylene **3b** with a bulky TIPS group could undergo bromination/oxycyclization to produce the mono-bromo product **7** along with a minor amount of bis-bromo product

Table 2. AgF-mediated bromination/oxycyclization of compounds **3a**, **3b**, and **9**.



3a: R = TMS
3b: R = TIPS
9: R = H
7 **8**

Entry	Substrate	NBS [equiv]	Solvent	*t* [h]	Yield [%][a]	**7**:**8**[b]
1	**3a**	1.1	MeCN	9	95 (**7**+**8**)	94:6
2	**9**	1.1	MeCN	8	83 (**7**+**8**)	91:9
3	**3b**	1.1	MeCN	11	82 (**7**+**8**)	91:9
4	**3b**	1.1	DMF	24	72 (**7**+**8**)	69:31
5	**3a**	2.5	MeCN	18	71 (only **8**)[c]	0:100
6	**3b**	2.5	MeCN	20	73 (only **8**)[c]	0:100

[a] Yields determined by GC analysis. [b] Product ratio was determined by GC and ^{1}H NMR spectroscopic analyses. [c] Yield of isolated product.

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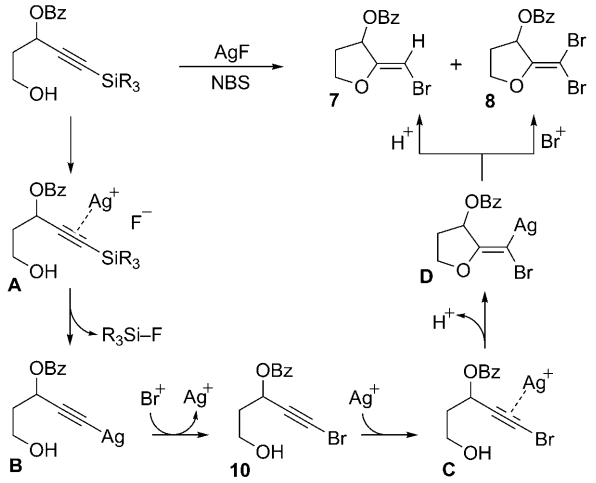
8 in a ratio of 91:9 (entry 3). The reaction with TIPS-acetylene **3b** in *N,N*-dimethylformamide (DMF) required a longer reaction time (entry 4), and this resulted in a lower product yield and selectivity than those obtained using acetonitrile as a solvent. When the reaction was conducted in acetone, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and dichloromethane, the starting material was primarily recovered. These failures could be due to the low solubility of AgF in these solvents.

Notably, the use of excess NBS (2.5 equiv) in the reaction of **3** with AgF in acetonitrile resulted in the formation of bis-bromo product **8** as the only detectable product (entries 5 and 6). In the absence of NBS, TIPS-protected acetylenic alcohol **3b** underwent smooth desilylative oxycyclization to give the corresponding nonhalogenated exocyclic enol ether in high yield (93%).

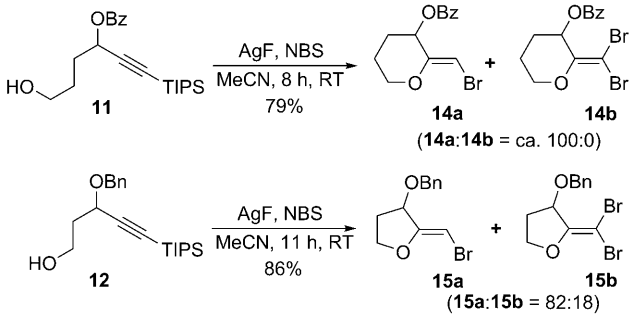
The formation of β-bromo enol ether **7** from **3** appears to occur via the intermediate bromoacetylene **10** (Scheme 3). During the reaction, we could observe bromoacetylene **10**,



Scheme 3. Proposed mechanism for the AgF-mediated tandem reaction.

and isolate this intermediate. When isolated **10** was treated with AgF, this compound readily cyclized, again resulting in bromo enol ether **7** in high yield (96%). These results together with the observed *Z* stereochemistry suggest a mechanism for the AgF-mediated tandem reaction (Scheme 3). The reaction could be initiated by the coordination of the silver ion to the silylated alkyne to form the π-alkynyl complex **A**. This coordination would favor nucleophilic displacement of the silyl group by silicophilic fluoride, thereby leading to the formation of the alkynyl silver **B**. The resulting alkynyl silver reacts with NBS to give the intermediate bromoacetylene **10**. When produced, the latter would be activated by silver ions again to form the π-alkynyl complex **C**. A subsequent *anti*-intramolecular addition of the alcohol group to the π-complex **C** would lead to the σ-complex **D**. The protonolysis of the carbon–silver bond in **D** with retention of configuration at the carbon atom would then liberate the β-bromo enol ether **7**. Alternatively, the bromolysis of **D** with NBS present in the reaction mixture would lead to the formation of β-dibromo enol ether **8**. The involvement of silver-vinylidene **D** during this sequence is supported by the observation that the isolated mono-bromo compound **7** was not transformed into the bis-bromo compound **8** upon treatment with NBS, regardless of the presence or absence of AgF.

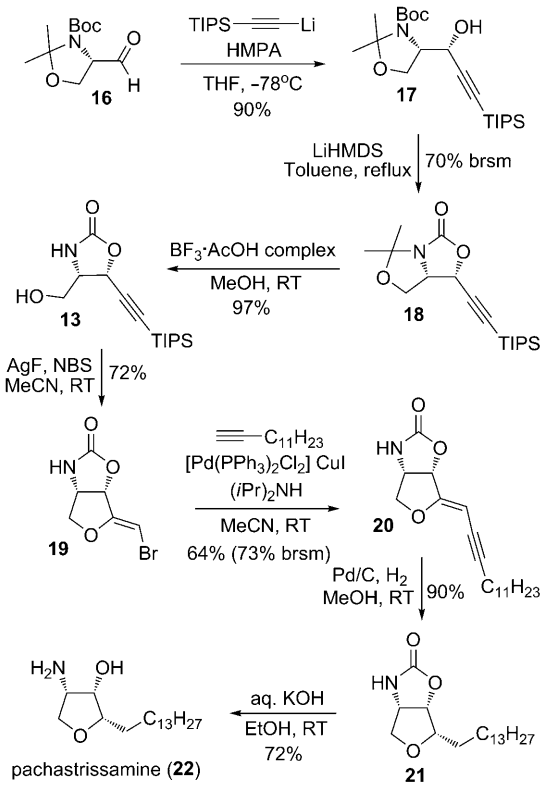
Although TMS has been used as a classical protecting group for terminal acetylenes, the bulkier TIPS protecting group is also very useful and attractive because of its stability under a wider range of reaction conditions. Thus, despite the observation that TMS-protected **3a** gave better yield and selectivity than TIPS-protected **3b** (Table 2, entry 1 vs. entry 3), TIPS-protected acetylenic alcohol was chosen to examine the scope of this tandem desilylative bromination/oxycyclization. We prepared the TIPS-protected acetylenic alcohols **11**, **12** (Scheme 4), and **13** (Scheme 5) and subjected them to the above-mentioned conditions. These reaction



Scheme 4. AgF-mediated bromination/oxycyclization of compounds **11** and **12**.

conditions were also found to be effective in the preparation of the functionalized pyran. The substrate **11** underwent an equally facile, AgF-mediated *exo*-selective tandem reaction to give pyran **14a** in 79% yield without notable formation of the bis-bromo product **14b**. Substrate **12**, bearing an electron-donating benzyl group, was also converted into the *exo*-dig tandem product **15**. The mono-bromide **15a** was the major product of the reaction; however, selectivity for the formation of mono-bromide **15a** and bis-bromide **15b** was lower than that for the benzoate-containing substrate **3**. Unlike **7**, isolated **15a** was somewhat unstable and decomposed gradually at room temperature. Substrate **13**, derived from (*S*)-Garner's aldehyde (**16**) over three steps (Scheme 5), readily cyclized to again yield the *Z* stereoisomer **19** along with a minor amount of bis-bromo product in a ratio of 81:19. These results suggested that the presented tandem reaction would be applicable to substrates with various functionalities although the product selectivity (mono- vs. bis-bromide) varies depending on the substrate type.

The exocyclic β-halo enol ether **19** was envisioned to be a useful starting point for the total synthesis of pachastrissamine[17,18] (**22**; Scheme 5) through cross-coupling reactions.



Scheme 5. Synthesis of substrate **13** and total synthesis of pachastrissamine from β-halo enol ether **19**. brsm = based on recovered starting material. HMPA = hexamethylphosphoramide; LiHMDS = lithium hexamethyldisilazane.

For this purpose, the obtained bromo-methylene **19** was subjected to Sonogashira conditions with tridec-1-yne.[19] The reaction occurred readily in acetonitrile[20] and gave the desired coupling product **20** in 64% yield (73% based on recovery of starting material) with complete retention of configuration. Full reduction of the enyne moiety in **20** with palladium/carbon under hydrogen furnished **21** with the desired configuration at C-1 as the sole diastereomer (90%). Finally, standard hydrolysis of **21** yielded the desired pachastrissamine (**22**) in 72% yield, the spectral data of which were in good agreement with those reported in the literature.[18b] Our total synthetic route for pachastrissamine from Garner's aldehyde is short and efficient owing to the tandem desilylative bromination/oxycyclization, and this route is also applicable to the preparation of pachastrissamine derivatives because various side chains may be introduced through cross-coupling reactions with the β-halo enol ether moiety in **19**.

In summary, we have developed a tandem method for the synthesis of exocyclic β-bromo enol ethers starting from easily accessible silyl-protected acetylenic alcohols. The AgF/NBS system is used to promote a tandem desilylative bromination/oxycyclization reaction at room temperature to give functionalized oxolane and oxane functionalities. This reaction preferentially provided a mono-bromo enol ether product in the presence of a slight excess of NBS, and a large excess of NBS afforded the bis-bromo product exclusively. As the exocyclic β-halo enol ether functionality could serve as a handle for further chemical transformations, this method is a valuable and efficient tool for the synthesis of natural or biologically active products. Further studies to expand the scope of this method as well as to develop its synthetic applications are now underway.

Experimental Section

General Procedure for Silver-Mediated Bromination/Oxycyclization (Table 2, entries 1–3)

NBS (1.1 equiv) and AgF (1.2 equiv) were added to a solution of acetylenic alcohol (0.2 mmol) in acetonitrile (4 mL, 0.05 M) in the dark. The reaction mixture was stirred at room temperature for 8–11 h, quenched with water, and extracted twice with EtOAc (15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and then filtered through a Celite pad. For analytical purposes, a small amount of the organic filtrate was subjected to GC analysis with dodecane as an internal standard. The crude product was purified using silica-gel column chromatography (EtOAc/hexane, 1:10) to afford the corresponding pure products **7** and **8**.

*(Z)-2-(Bromomethylene)-tetrahydrofuran-3-yl benzoate (**7**)*

White solid: m.p. 80.1–82.5 °C; IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 2903, 1719, 1667, 1451, 1253 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz): δ = 8.01 (d, J = 7.6 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.6 Hz, 2H), 5.53 (t, J = 4.1 Hz, 1H), 5.45 (s, 1H), 3.81 (td, J = 8.2, 8.0 Hz, 1H), 3.67–3.62 (m, 1H), 1.58–1.53 ppm (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): δ = 165.5, 157.2, 133.2, 130.2, 130.0 (2C), 128.6 (2C), 79.1, 73.1, 69.4, 32.5 ppm; MS (FAB): m/z: 285 (30), 283 ($[M+H]^+$, 32), 203 (34), 154 (100); HRMS (FAB): calcd for $C_{12}H_{12}BrO_3$: 282.9892 ($[M+H]^+$); found: 282.9970.

*2-(Dibromomethylene)-tetrahydrofuran-3-yl benzoate (**8**)*

White solid: m.p. 90.6–94.5 °C; IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 2903, 1721, 1601, 1451, 1276 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz): δ = 8.09 (d, J = 7.2 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.6 Hz, 2H), 5.95 (t, J = 3.9 Hz, 1H), 3.79–3.73 (m, 1H), 3.62–3.57 (m, 1H), 1.62–1.57 ppm (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): δ = 165.3, 156.1, 133.3, 130.1 (2C), 130.0, 128.7 (2C), 73.7, 71.1, 67.0, 33.2 ppm; MS (FAB): m/z: 364 (35), 362 (68), 360 ($[M]^+$, 35), 241 (100); HRMS (FAB): calcd for $C_{12}H_{10}Br_2O_3$: 359.8997 ($[M]^+$); found: 359.8997.

Acknowledgements

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